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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,188	06/02/2005	Niall Gormley	2713-1-015PCT/US	1232
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KLAUBER & JACKSON 411 HACKENSACK AVENUE HACKENSACK, NJ 07601			EXAMINER SHAW, AMANDA MARIE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/537,188	Applicant(s) GORMLEY ET AL.	
	Examiner AMANDA SHAW	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 April 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4 and 27-32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4 and 27-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 02 June 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>4/4/2008</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is in response to the amendment filed April 4, 2008. This action is made FINAL.

Claims 4 and 27-32 are currently pending. Claim 4 has been amended. Claims 27-32 are newly presented.

Withdrawn Objections

2. The objections made to the specification in the Office Action of October 18, 2007 are withdrawn since the Applicants have filed a paper sequence listing, a computer readable format of the sequence listing, and a statement that the content of the paper and computer readable sequences are the same

Withdrawn Rejections

3. The rejection made under 35 USC 112 2nd paragraph in section 4 of the Office Action of October 18, 2007 is withdrawn in view of amendments made to the claims.

The rejections made under 35 USC 103(a) in sections 6 and 7 of the Office Action of October 18, 2007 are withdrawn in view of the amendments made to claim 4 and the cancellation of claim 5. Specifically the claims have been amended to require an array of immobilized single stranded template molecules wherein the density of immobilized single stranded template nucleic acid molecules is 10^6 - 10^9 different template sequences per cm^2 . However new art rejections are set forth below.

Claim Objections

4. Claim 28 is objected to because of the following informalities: claim 28 depends from itself, however it appears that it should depend from claim 27. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4 and 27-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 27-32 recite the limitation "the complementary synthetic strand". There is insufficient antecedent basis for this limitation in the claims because although the claims previously refer to "synthesizing a complementary strand" they do not refer to a "complementary synthetic strand".

Claims 4 and 27-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that the goal of the method and the final step do not agree. The claims are drawn to method for reducing sequencing errors by sequencing, recovering, and resequencing a single stranded template nucleic acid. However, the claims recite the final step of performing a second round of sequencing. The steps listed in the method do not result in the reduction of sequencing errors by sequencing, recovering,

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and resequencing. For instance it is noted that the claims do not even have a step of recovering. Further it is unclear how comparison of the first and second rounds of sequencing reduces sequencing errors especially since the claims do not have an active step of "comparing".

Claims 27 and 29 recites the limitation "the template polynucleotides". There is insufficient antecedent basis for this limitation in the claims because although the claims previously refer to a "single stranded template nucleic acid molecules" it does not refer to a "template polynucleotide".

Claim 28 recites the limitation "the double stranded anchor". There is insufficient antecedent basis for this limitation. This rejection may be overcome by amendment of claim 28 to depend from claim 27.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

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not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 4, 27-29, and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balasubramanish (WO 01/57248 Pub 9/2001) as evidenced by Cheeseman (US Patent 5302509 Issued 1994) and in view of Lackey (US Patent 5652126).

Balasubramanish teaches a method comprising forming an array of polynucleotide molecules immobilized on a solid surface. Each polynucleotide has a hairpin loop structure wherein one end of hairpin loop structure acts as a primer and the other end of the hairpin loop structure acts as a template (page 3, lines 11-14 and page 4 line 28 to page 5 line 7). Balasubramanish further teaches that the polynucleotides are attached to the array at a density of between 10^6 - 10^9 sequences per cm^2 . Balasubramanish also teaches determining the sequence of the template nucleic acid by synthesizing a complementary nucleic acid strand. Specifically Balasubramanish cites the method of Cheeseman as a suitable sequencing method (page 7, lines 24-31). The method of Cheeseman comprises contacting the template with fluorescently labeled 3' blocked nucleotide triphosphates, with each of the bases having a different fluorescent label and a polymerase. The DNA polymerase causes selective addition of only the complementary labeled NTP, thus identifying the next unpaired base in the

unknown strand. The 3' blocking group is then removed, setting the system up for the next NTP addition and so on (Abstract).

Regarding Claim 4 Balasubramanish does not teach a method further comprising removing the complementary nucleic acid strand and performing a second round of sequencing. Regarding Claim 29 Balasubramanish does not teach that the primer has a recognition site for a restriction endonuclease.

However Lackey teaches a method that comprises synthesizing a complementary copy nucleic acid sequence using a template sequence. Lackey further teaches when a DNA primer/template with a single 3' ribonucleotide is used, cleavage at the ribonucleotide residue, followed by separation and purification of the oligonucleotide product, results in a fully regenerated and reusable primer/template (Col 13, lines 26-31). Thus Lackey teaches removing the complementary nucleic acid strand and performing a second round of synthesizing a complementary copy of the template sequence. Lackey further teaches that cleavage may be performed using a site specific restriction endonuclease, alkaline hydrolysis or an endonuclease such as RNase (col 12, lines 42-47). Thus Lackey teaches a method wherein the primer has a recognition site for a restriction endonuclease.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Balasubramanish by removing the complementary strand and resequencing the template as suggested by Lackey. One of skill in the art would have been motivated to remove the complementary strand and resequence the template for the benefit of verifying the

results from the first sequencing reaction. Further methods in which the primer/template are reusable are most cost effective. Additionally since all of the claimed method steps were known in the art, one of skill could have combined these methods and the combination would have yielded predictable results.

Regarding Claims 27 and 28 Balasubramanish teaches a method wherein the template polynucleotides are attached to a double stranded anchor wherein the double stranded anchor is a complementary hairpin (page 4 line 28 to page 5 line 7).

Regarding Claim 30 Balasubramanish teaches that the templates are individually resolvable (page 4, line 11).

Regarding Claim 31 Balasubramanish teaches a method wherein the sequencing determination is carried out using cycles of incorporation and detection of fluorescently labeled nucleotides. Specifically Balasubramanish refers to the method of Cheeseman which teaches this (see Cheeseman abstract).

8. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Balasubramanish (WO 01/57248 Pub 9/2001) as evidenced by Cheeseman (US Patent 5302509 Issued 1994) in view of Lackey (US Patent 5652126) as applied to claims 4 and 31 above and in further view of Barnes (WO 01/57249 Pub 8/2001).

The teachings of Balasubramanish, as evidenced by Cheeseman and Lackey are presented above.

The combined references do not teach a method wherein the fluorescent nucleotides are detected using a microscope with total internal reflection based imaging.

However Barnes teaches that using total internal reflection fluorescent microscopy it is possible to achieve wide field imaging with single polymer sensitivity. This allows arrays of greater than 10^7 resolvable polymers per cm^2 to be used (page 6, lines 9-14).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Balasubramanish and Lackey by using a microscope with total internal reflection to detect the incorporation of each nucleotide as suggested by Barnes particularly since Barnes teaches it is possible to achieve wide field imaging with single polymer sensitivity and that this allows arrays of greater than 10^7 resolvable polymers per cm^2 to be used. Therefore it would have been obvious to use the detection method disclosed by Barnes for the benefit of being able to detect a large number of individual fluorescent nucleotides present on the array.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Carla Myers/
Primary Examiner, Art Unit 1634

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